

REMARKS

In the above Preliminary Amendment, claims 1-58 and 63-64 have been canceled without prejudice. Pursuant to the Restriction Requirement issued in the parent application on September 30, 1999, Applicants are pursuing claims directed to methods of inducing apoptosis and methods of treatment in the instant divisional application.

Claims 59-62 have been amended, and Claims 65-97 have been added to further exemplify embodiments provided by claims 59-62, as filed. Support for the added claims can be found, for example, on pages 9, 13, 14, 16-19, 50-55, and 59-61 of the specification, and accordingly, no new matter has been introduced.

The amendments are illustrated in the attached paper entitled "MARKED UP VERSION TO SHOW CHANGES MADE." For the Examiner's convenience, a clean copy of the now pending claims 59-62 and 65-97 is provided above.

Respectfully submitted,
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IN THE SPECIFICATION:

On page 1, under the title of the invention, in the paragraph on lines 10-14, the text has been amended as follows:

-- This application is a divisional application of non-provisional application serial no. 09/079,029, now pending, claiming priority under Section 119(e) to provisional application number 60/046,615 filed May 15, 1997 and provisional application number 60/074,119 filed February 9, 1998, the contents of which are hereby incorporated by reference. --

IN THE CLAIMS:

Please cancel claims 1-58 and 63-64 without prejudice.

Claims 59-62 have been amended as follows:

59. (Amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of [the Apo-2 agonistic antibody of claim 29] monoclonal antibody which (a) binds to Apo-2 polypeptide consisting of the contiguous amino acid residues 1 to 411 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cancer cell in vivo or ex vivo.

60. (Amended) The method of claim 59 wherein said [agonistic] antibody comprises a single-chain antibody.

61. (Amended) A method of treating mammalian cancer cells comprising exposing mammalian cancer cells to [an agent which activates Apo-2] an effective amount of monoclonal antibody which (a) binds to Apo-2 polypeptide consisting of the contiguous amino acid residues 1 to 411 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cancer cell in vivo or ex vivo.

62. (Amended) The method of claim 61 wherein said [agent comprises an agonistic Apo-2] antibody comprises a single-chain antibody.

The following claims have been added:

--65. A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cell *in vivo* or *ex vivo*.

66. A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 1 to 182 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cell *in vivo* or *ex vivo*.

67. A method of treating mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of monoclonal antibody which ~~(a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide~~ consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cell *in vivo* or *ex vivo* ..

68. A method of treating mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 1 to 182 of SEQ ID NO:1 and (b) stimulates apoptosis in at least one type of mammalian cell *in vivo* or *ex vivo*

69. The method of claim 59, 65, or 66, wherein said antibody is a chimeric antibody.

70. The method of claim 59, 65, or 66, wherein said antibody is a humanized antibody.

71. The method of claim 59, 65, or 66, wherein said antibody is a human antibody.

72. The method of claim 59, 65, or 66, wherein said antibody comprises an Fab fragment.

73. The method of claim 59, 65, or 66, wherein said antibody comprises a scFv fragment.

74. The method of claim 59, 65, or 66, wherein said antibody comprises a F(ab')₂ fragment.

75. The method of claim 59, 65, or 66, wherein said antibody binds to the same epitope as the epitope to which the monoclonal antibody produced by the hybridoma cell line deposited as ATCC accession number HB-12456 binds.

76. The method of claim 59, 65, or 66, wherein said antibody comprises the 16E2 antibody.

77. The method of claim 59, 65, or 66, wherein said antibody comprises the 20E6 antibody.

78. The method of claim 59, 65, or 66, wherein said antibody comprises the 24C4 antibody.

79. The method of claim 59, 65, or 66, wherein said antibody is fused to an epitope tag sequence.

80. The method of claim 59, 65, or 66, wherein the cancer cells are colon or colorectal cancer cells.

81. The method of claim 59, 65, or 66, wherein the cancer cells are lung cancer cells.

82. The method of claim 59, 65, or 66, wherein the cancer cells are breast cancer cells.

83. The method of claim 61, 67, or 68, wherein said antibody is a chimeric antibody.

84. The method of claim 61, 67, or 68, wherein said antibody is a humanized antibody.

85. The method of claim 61, 67, or 68, wherein said antibody is a human antibody.

86. The method of claim 61, 67, or 68, wherein said antibody comprises an Fab fragment.

87. The method of claim 61, 67, or 68, wherein said antibody comprises a scFv fragment.

88. The method of claim 61, 67, or 68, wherein said antibody comprises a F(ab')₂ fragment.

89. The method of claim 61, 67, or 68, wherein said antibody binds to the same epitope as the epitope to which the monoclonal antibody produced by the hybridoma cell line deposited as ATCC accession number HB-12456 binds.

90. The method of claim 61, 67, or 68, wherein said antibody comprises the 16E2 antibody.

91. The method of claim 61, 67, or 68, wherein said antibody comprises the 20E6 antibody.

92. The method of claim 61, 67, or 68, wherein said antibody comprises the 24C4 antibody.

93. The method of claim 61, 67, or 68, wherein said antibody is fused to an epitope tag sequence.

94. The method of claim 61, 67, or 68, wherein said mammalian cancer cells are exposed to chemotherapy or radiation therapy.

95. The method of claim 61, 67, or 68, wherein the cancer cells are colon or colorectal cancer cells.

96. The method of claim 61, 67, or 68, wherein the cancer cells are lung cancer cells.

97. The method of claim 61, 67, or 68, wherein the cancer cells are breast cancer cells. --